REMARKS

I. STATUS OF INTERFERENCE NO. 105,188 BETWEEN INSTANT APPLICATION AND U.S. PATENT NO. 6,479,258 ISSUED TO SHORT.

On October 13, 2003, Applicants filed a Request for Interference with the USPTO, requesting that an interference be declared between the instant application USSN 09/724,869 to Juha Punnonen et al., which is assigned to Maxygen, Inc., and U.S. Patent No. 6,479,258 ("the '258 patent"), which issued on November 12, 2000 to Jay M. Short based on USSN 09/495,052 filed January 31, 2000. The '258 patent is assigned on its face to Diversa Corporation.

On January 23, 2004, the USPTO Board of Patent Appeals and Interferences ("BPAI") issued a Notice Declaring Interference (37 CFR § 1.661) between the instant application and the '258 patent. The interference was designated Interference No. 105,188. The Board accepted Applicants' proposed Count, which was identical to claim 47 of the instant application, and designated claim 47 and claims 1-86 of the '258 patent as corresponding to the Count. The Board designated Punnonen et al. as Senior Party and Short as Junior Party.

Short's USSN 09/495,052 application, which ultimately issued as the '258 patent, was filed just over five months after the following four PCT applications assigned to Maxygen published on August 19, 1999: WO 99/41368, WO 99/41402, WO 99/41383, and WO 99/41369. Each these PCT applications names Juha Punnonen as the lead inventor and for convenience are designated the "Punnonen PCT applications." Significantly, the specification and original claims of the instant application USSN 09/724,869 are identical to the specification and claims published in Punnonen's WO 99/41368. As discussed in detail in numerous briefs filed by Senior Party Punnonen during the Interference, the majority of text and figures in the Short '258 patent were copied directly from the four Punnonen PCT applications. In addition, the originally filed claims in the '258 patent were substantially copied from the published claims of Punnonen's WO 99/41368. No Information Disclosure Statement was filed in the '258 patent, and the fact that the text and figures of the '258 patent were copied from Maxygen's previously published PCT applications was not brought to the Examiner's attention. The Examiner was not apprised of the significance of the four Punnonen PCT

applications. Nor was the Examiner informed that the claims Short presented for examination – and which ultimately issued in the '258 patent – were substantially copied from Punnonen's application.

On November 25, 2005, the Board issued Decision – Motions – Bd.R. 125a(a) in the Interference ((Paper No. 181) [hereinafter "Decision"], ruling that claim 47 of the instant application was patentable and that the majority of the claims in the '258 patent were unpatentable.

On April 7, 2006, the Board issued Order – Bd.R. 104(a) – Miscellaneous (Paper No. 196), stating that Junior Party Short had abandoned the interference and explaining that such abandonment was the equivalent of a request for adverse judgment.

This Order also expressly noted that Short had promised to file a paper dedicating claims 1-88 of related U.S. Patent No. 6,713,279 ("the '279 patent) to the public. The '279 patent, which issued to Jay Short on March 30, 2004, is assigned on its face to Diversa Corporation. The '279 patent is based on USSN 09/498,557, filed February 4, 2000, which is a continuation-in-part of USSN 09/495,052 (now the '258 patent). As in the '258 patent, the majority of text and figures in Short's '279 patent were copied from the four Punnonen PCT applications, and claims 1-88 of the '279 patent were substantially copied from the claims published in Punnonen's WO 99/41368 – which is identical to the instant application USSN 09/724,869. Here, too, the fact that most of the '279 patent was copied directly from Maxygen's previously published PCT applications was not brought to the Examiner's attention. The Examiner was not made aware of the significance of the four Punnonen PCT applications and was not informed that claims 1-88 presented by Short for examination were substantially copied from Punnonen. In its Order, the Board recommended that Short file its disclaimer of the '279 patent directly in the record for the '279 patent rather than send it through the Board. To Applicants' knowledge, Short (Diversa) has not yet filed any such disclaimer in the '279 patent record.

On April 21, 2006, the Board entered Judgment – Bd.R. 127(b) – Requested (Paper No. 198), ordering that adverse judgment be entered against Short and that claims 1-86 of the '258 patent be canceled. The Judgment also ordered that Punnonen's instant application 09/724,869 be remanded to the Examiner for further examination and surprisingly recommended that the Examiner reject Punnonen's pending claim 47 (which the Board had previously found patentable in its November 25,

2005 Decision) for the new reasons presented in a separately entered "Memorandum in Support of Recommendation" [hereinafter "Memorandum"] (Paper No. 199) – also dated April 21, 2006.

The application was subsequently remanded to Examiner Teresa Wessendorf for further examination. On September 6, 2006, Examiner Wessendorf issued a non-final Office Action rejecting claim 47 under 35 U.S.C. § 103(a) as allegedly being unpatentable for the reasons set forth in the BPAI Memorandum.

II. STATUS OF THE CLAIMS.

Claims 1-46 and 48 were canceled prior to the initiation of the Interference. Claim 47 – Applicants' sole claim in the Interference – has been canceled herein without prejudice to subsequent renewal. New claim 49 has been added.

In the Remarks that follow, Applicants discuss both claim 47 (now canceled herein) and new claim 49. For the convenience of the Examiner, both claims are reproduced below:

> 47. (Canceled) A method for obtaining an immunomodulatory polynucleotide that has an optimized modulatory effect on an immune response as compared to the response prior to optimization, or encodes a polypeptide that has an optimized modulatory effect on an immune response as compared to the response prior to optimization, the method comprising:
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> a) creating a library of recombinant polynucleotides; and
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> b) screening the library to identify an optimized recombinant polynucleotide that has, or encodes a polypeptide that has, a modulatory effect on an immune response induced by a vector;
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> wherein the optimized recombinant polynucleotide or the polypeptide encoded by the recombinant polynucleotide exhibits an enhanced ability to modulate an immune response compared to a polynucleotide from which the library was created;
>
> wherein said optimized modulatory effect on an immune response is induced by a genetic vaccine vector, wherein the optimized recombinant polynucleotide encodes a co-stimulator selected from B7-1 (CD80) or B7-2 (CD86) and the screening step involves selecting variants with altered activity through CD28 or CTLA-4,
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> and whereby optimization is achieved by recursive sequence recombination.

49. (New) A method for obtaining an optimized immunomodulatory polynucleotide, comprising:

a) creating a library of mutant polynucleotides from (1) a set of one or more nucleic acids encoding a B7-1 (CD80) protein or (2) a set of one or more nucleic acids encoding a B7-2 (CD86) protein, wherein nucleic acids of the set differ from each other in at least two nucleotides; and

b) screening the library to identify an optimized mutant polynucleotide that encodes a mutant B7-1 or mutant B7-2 protein which is a costimulator having (1) an improved ability to activate a T cell response induced by a genetic vaccine vector, (2) an increased activity through CD28, and (3) a decreased activity through CTLA-4 compared to a B7-1 or B7-2 protein encoded by a nucleic acid from which the library was created;

whereby optimization is achieved by recursive sequence recombination.

New claim 49 is fully support by the specification as filed and presents no new matter. Support for claim 49 is provided throughout the specification, including at, but not limited to, e.g., claim 47; original claims 1 and 4; p. 49, line 15 to p. 53, line 20; p. 66, line 16 to p. 68, line 23; p. 11, lines 3-11; p. 17, line 1 to p. 19, line 25.

III. REJECTION UNDER 35 USC § 103.

The Examiner rejects claim 47 under 35 U.S.C. § 103(a) as allegedly being *prima facie* obvious over the combined teachings of WO 95/03408 ("the Freeman PCT"), WO 91/16427 ("the Short PCT"), and Stemmer, "Searching Sequence Space," *Biotechnol.* 13:549-553 (1995) ["Stemmer reference"] for the reasons set forth in the BPAI Memorandum. The Examiner does not reiterate the Board's reasons in the Office Action, but simply references the Board's conclusion in its Memorandum. Although the rejection of claim 47 has been mooted by its cancellation, Applicants strongly traverse the Board's conclusion that claim 47 is obvious over these references and believe it is important to address the errors in the Board's analysis so that the record is made clear.

As noted above, Applicants traverse the rejection of claim 47, but Applicants further submit that such rejection is nevertheless overcome by new claim 49. As demonstrated below, new claim

49 is plainly patentable over the combined teachings of the Freeman PCT, the Short PCT, and/or the Stemmer reference.

A. The Board's Revised Findings in its "Memorandum" Regarding the Patentability of Claim 47 and the Teachings of the Freeman PCT and the Short PCT Are Wholly Incorrect.

In its original Decision (Paper No. 181) in the Interference, the Board found that claim 47 was patentable over the prior art of record. See BPAI Decision (Paper No. 181), e.g., ¶¶170-185 at p. 142, line 1 to p. 149, line 22. Applicants agree with the Board's original conclusion regarding the patentability of claim 47 and the analysis presented in the Board's original Decision (Paper No. 181) on which it based this conclusion. The Board's original Decision was drafted by Administrative Patent Judge Carol A. Spiegel and signed by Administrative Patent Judges Spiegel, Richard E. Schafer, and Richard Torczon and reflects a comprehensive review of the entire record of the lengthy Interference proceedings. This panel of three judges considered and weighed all of the evidence and arguments made of record during the Interference, including, e.g., numerous preliminary and miscellaneous motions, declaratory and documentary evidence, and legal and factual arguments submitted by both parties. These three judges were also present at the oral hearing held on November 3, 2004 in which both parties' representatives orally argued their respective positions and took questions put forward by the panel. The original Decision (Paper No. 181), which is 158 pages in length, constitutes a thorough and well-reasoned evaluation of the entire record before this panel.

Applicants believe that the Board's original Decision (Paper No. 181) provides a correct construction of claim 47 in light of Applicants' specification, a proper analysis of the evidence of record, and an accurate interpretation of the teachings of the Freeman PCT and the Short PCT. Applicants submit that the original Decision properly determined that claim 47 was patentable.

In its subsequent "Memorandum" (Paper No. 199),[1] entered over four months after the Board's original Decision (Paper No. 181), the Board unexpectedly reversed itself, stating that its

[1] The Board termed this paper (Paper No. 199) a "Memorandum in Support of Recommendation" and recommended that the Examiner further examine claim 47 in light of the Board's views expressed therein. The Board did not designate this paper a "Decision".

original Decision had focused only on the preferred embodiments of the Freeman PCT and the Short PCT and their shortcomings relative to the subject matter defined by claim 47. Upon reconsideration of the complete disclosures of the Freeman and Short PCTs, in light of the Stemmer reference's description of the state of the art, the Board found claim 47 to be obvious.

This subsequent Memorandum (Paper No. 199), which is 28 pages in length, was drafted by Administrative Patent Judge Teddy S. Gron. Judges Schafer and Torczon joined Judge Gron in signing the Memorandum. Judge Gron had not participated up to that point in any matter in the Interference and was not present at the oral hearing. The Board offered no reason as to why Judge Gron – despite not having been involved in the Interference – was assigned the job of drafting the Memorandum. Notably, the analysis presented in the Memorandum appears divorced from the Interference record. Little, if any, consideration seems to have been given to the extensive evidence made of record through the numerous preliminary and miscellaneous motions and oral hearing regarding the proper construction of claim 47 and the proper interpretation of the teachings of the Freeman and Short PCTs. Significantly, the terms recited in claim 47 are not construed in light of Applicants' specification and its teachings; the application and its teachings are effectively ignored. Simply put, the Memorandum does not reflect a carefully reasoned and accurate evaluation of the Interference record.

Applicants respectfully traverse the Board's findings as set forth in this Memorandum (Paper No. 199). As demonstrated below, in the Memorandum, claim 47 is not construed properly based on Applicants' specification, the evidence of record is effectively ignored, and the teachings of the Freeman PCT and the Short PCT are misinterpreted.

1) The Freeman PCT Does Not Teach or Suggest Any of the Limitations of Canceled Claim 47.

In its original Decision, the Board correctly determined that the Freeman PCT does not teach or suggest the limitations of the method defined by claim 47. See BPAI Decision (Paper No. 181), e.g., ¶147 at p. 128, line 30 to p. 129, line 7; ¶149 at p. 132, line 17 to p. 134, line 2; ¶170 at p. 142, lines 1-9. In its subsequent Memorandum, the Board finds that the Freeman PCT teaches or suggests all of the limitations of the method of claim 47 – except the limitation "whereby optimization by

recursive sequence recombination." BPAI Memorandum (Paper No. 199), p. 24, lines 10-15. Applicants agree that the Freeman PCT does not teach or suggest recursive sequence recombination. However, Applicants strongly disagree with the Board's view that the Freeman PCT discloses the remaining limitations of claim 47. *Id.* As shown below, in its analysis the Board repeatedly overlooks or disregards one or more of the specific limitations recited in the claimed method.

The Board now takes the position the Freeman PCT describes "procedures...for obtaining new polynucleotides [which] comprise the steps of: a) creating a library comprising recombinant polynucleotides, and b) screening the library to identify polynucleotides which encode B7-1 and/or B7-2 variants having altered modulatory effects on an immune response, whether the effects are enhanced immune responses or inhibited immune responses to a vaccine vector." BPAI Memorandum, p. 11, lines 2-9. In support of these assertions, the Board cites passages in the Freeman PCT describing the construction of a cDNA library from natural human splenic B cells or murine M12 cells and screening such library to obtain human or murine B7-2. See Memorandum, p. 11, line 9 to p. 12, line 30 (citing the Freeman PCT, p. 18, line 27 to p. 19, line 20 (II. Isolation of mRNA and Construction of cDNA Library); p. 70, line 11 to p. 72, line 4 (Example 4: Cloning, Sequencing and Expression of the B7-2 Antigen, A. Construction of cDNA Library); p. 78, line 17, to p. 80, line 6 (Example 6, Cloning and Sequencing of the Murine B7-2 Antigen, A. Construction of cDNA Library; p. 19, line 23 to p. 20, line 6 (III. Transfection of Host Cells and Screening for Novel B Lymphocyte Activation Antigens); p. 72, lines 6-32 (Example 4, B. Cloning Procedure [for human B7-2]); p 80, lines 8-34 (Example 6, B. Cloning Procedure [for murine B7-2]).

Applicants respectfully submit that the Board's conclusions in the Memorandum are flawed. These passages in the Freeman PCT do not teach or suggest creating a library of recombinant (mutant) polynucleotides encoding mutant B7-1 or mutant B7-2 proteins and screening such library for an optimized mutant B71- or B7-2 protein[2] that functions as a costimulator and has an enhanced ability to modulate an immune response induced by a genetic vaccine vector compared to a

[2] Based on the definition and use of the word "recombinant" in the instant application, the terms "recombinant polynucleotide" and "recombinant polypeptide" in claim 47, properly read, do not refer to wild-type polynucleotides and polypeptide, but rather to mutant progeny polynucleotides and polypeptides generated by mutagenesis methods. See e.g., the instant application, including at, but not limited to, e.g., p. 11, lines 3-11; p. 17, line 1 to p. 19, line 29; original claim 4. New claim 49 eliminates any confusion in this regard by substituting the term "mutant" for the term "recombinant."

polynucleotide from which the library was created (explicitly set forth in claim 47). Rather, these passages merely describe well-known procedures for cloning wild-type genes from mammalian cells.

At the time the Freeman PCT was filed, the nucleotide and amino acid sequences of human B7-1 were known. Freeman's work involved the discovery of a different B7 molecule – B7-2 – and the Freeman PCT simply discloses the process Freeman used to clone the wild-type human B7-2 gene and the murine B7-2 gene. For example, to clone the wild-type human B7-2 gene from human splenic B cells, Freeman describes preparing a cDNA library which contains DNA molecules that are DNA copies of the many different types of mRNA molecules naturally present in the human splenic B cells. Freeman PCT, p. 18, line 27 to p. 19, line 20; p. 70, line 11 to p. 72, line 4. This cDNA library is not a library of mutant molecules, but a collection of DNA molecules that are copies of the many different naturally occurring mRNA molecules in human B cells. Because the cDNA library prepared from human B cells includes many different human DNA sequences (corresponding to the many different human mRNA sequences naturally present in human B cells), the library must be screened to identify and isolate the human gene of interest – in this case, the human B7-2 gene – from the other human genes. To identify the human B7-2 gene, Freeman describes screening the human cDNA library by transfecting cells with the human cDNA library and expressing all of the proteins encoded by the human cDNA molecules on the cells. Transfectants expressing human B7-1 are then removed with an anti B7-1 monoclonal antibody. Transfectants expressing human B7-2 are positively selected by reaction with CD28Ig and CTLA-4Ig (CD28 and CTLA-4 are known ligands for B7-1), followed by panning with anti-human Ig antibody coated plates. After panning, episomal DNA is recovered from the panned cells and transformed into a bacterial host. Plasmid DNA is reintroduced into COS cells and the cycle of expression and panning is repeated to better separate human B7-2 from many other expressed proteins. *Id.*, p. 19, line 23 to p. 20, line 6; p. 72, lines 6-32. The wild-type human B7-2 gene is then isolated from the selected cells, and its nucleic acid sequence and protein sequence are determined. *Id.*, p. 72, line 34 to p. 74, line 30.

The Freeman PCT similarly describes the cloning of the murine B7-2 sequence from murine M12 cells by using these standard expression cloning techniques. Here, too, the murine cDNA library is not a library of mutant molecules, but simply a collection of DNA molecules representing

copies of the many different mRNA molecules in murine M12 cells. *Id.*, p. 78, line 17 to p. 80, line 34. No optimized mutant polynucleotide encoding a costimulator mutant B7-2 protein having an enhanced ability to modulate an immune response compared to, e.g., a wild-type B7-2 protein is described. Freeman merely describes the isolation and identification of the murine B7-2 gene encoding murine B7-2 protein.

The Board also finds that the Freeman PCT describes a method "for obtaining an immunomodulatory polynucleotide that encodes a B7-2 antigen which has an altered modulatory effect on an immune response induced by a genetic vaccine vector as compared to the response to the unaltered antigen [which] comprises: a) creating a library of DNA encoding a natural B7-2 antigen and DNA altered to encode a B7-2 variant having a reduced activity or enhanced inactivity; b) inducing homologous recombination between the natural DNA and the altered DNA comprising a DNA library; and c) screening all new DNA resulting from homologous recombination of natural DNA and altered DNA comprising the DNA library for expression of B7-2 variants which reduce the animal's immune response to a vaccine as compared to its natural immune response." BPAI Memorandum, p. 12, line 31 to p. 13, line 9. In support of this finding, the Board cites p. 22, line 17 to p. 23, line 17 of the Freeman PCT, emphasizing in particular p. 22, line 33 to p. 23, line 17.

Applicants respectfully submit that this cited passage is of no relevance to the method defined by claim 47 (or new claim 49). This passage describes making a B7-2 "knock out" animal that has no functional B7-2 gene. In this example, the animal's endogenous B7-2 gene is deleted or replaced by another gene (such as a selectable marker). Freeman PCT, p. 22, line 33 to p. 23, line 17. Because the animal has no functional endogenous B7-2 gene, it cannot produce a functional B7-2 protein that acts as a costimulator. Freeman does not suggest whatsoever that the animal produces a mutant B7-2 protein that is a <u>costimulator</u> having an <u>enhanced ability</u> to modulate an immune response compared to the animal's original wild-type B7-2. A "knock out" animal may have an altered immune function, but this would be due to the lack of a functional B7-2 gene encoding a functional B7-2 protein – not to the altered activity of any mutant B7-2 protein.

The Board further contends that the Freeman PCT teaches that "optimization may be achieved by homologous recombination of DNA comprising a library of DNA including endogenous and altered B7-2 DNA." BPAI Memorandum, p. 15, lines 18-21. This assessment of Freeman's

teachings is not only wrong – it has no bearing on the method defined by claim 47 (or new claim 49).[3] First, the homologous recombination procedure described in Freeman is irrelevant to Applicants' methods. Freeman simply describes using a well-known homologous recombination procedure to introduce a portion of genomic DNA that lacks a functional B7-2 gene into a stem cell line so as to generate an embryo that is ultimately brought to term to create a "knock out" animal lacking any functional B7-2. *Id.*, p. 23, lines 1-17. Freeman does not suggest using any recombination procedure to generate an optimized functional mutant B7-2 protein that is a costimulator having an enhanced ability to modulate an immune response (or an improved ability to activate a T cell response) compared to, e.g., a wild-type B7-2.

Second, in this passage, the Freeman PCT does not describe making a library of mutant polynucleotides encoding mutant B7-2 proteins, as in Applicants' methods. Even if the endogenous B7-2 DNA sequence in the stem cell line and the sequence of genomic DNA lacking a functional B7-2 gene inserted into the homologous recombination vector were deemed to constitute a "library" of DNA – which Applicants do not admit – such a library is not a library of mutant B7-2 DNA molecules.

Third, this passage does not describe any method for making an optimized B7-2 that properly functions as a costimulator. On the contrary, Freeman simply describes making a "knock out" animal which lacks and is thus incapable of costimulating an immune response.

The Board further alleges that the Freeman PCT discloses procedures for obtaining new polynucleotides encoding active B7-2 co-stimulator variants having an enhanced ability to modulate an immune response induced by a genetic vaccine vector and having altered activity through CTLA-4 and/or CD28 as compared to a predecessor B7-2 molecule, such as a wild-type B7-2. BPAI Memorandum, p. 9, line 41 to p. 10, line 4. The Board asserts that Freeman discloses new polynucleotides encode proteins that upregulate immune response by either inhibiting delivery of a costimulatory signal to T cells or enhancing delivery of a costimulatory signal to T cells and points to soluble multivalent forms of B7-2 as examples of altered B7-2 antigens.

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[3] The Board does correctly recognize that the homologous recombination procedure described in the Freeman PCT has nothing to do with recursive sequence recombination, as defined by the instant application and as set forth in canceled claim 47 and new claim 49.

The problem with these allegations is that they have nothing to do with the specific method defined by claim 47 (or new claim 49). Applicants agree that the Freeman PCT discloses methods for cloning wild-type human B7-2 and murine B7-2. Applicants also agree that the Freeman PCT discloses methods for making soluble fusion protein forms of human B7-2 (i.e., B7-2-Ig) comprising the extracellular domain of human B7-2 linked to an Ig domain. However, the fact that Freeman discloses cloning the human B7-2 gene from a human cDNA library or the murine gene from a murine B7-2 cDNA library or making soluble fusion proteins from either cloned B7-2 gene does not mean Freeman discloses the particular method recited in claim 47 (or claim 49). Simply put, Freeman does not disclose any method involving making a library of mutant polynucleotides encoding B7-2 proteins and screening such library to identify a B7-2 mutant *that is a costimulator* having an enhanced ability to modulate an immune response induced by a genetic vaccine, as compared to a library used to make the method.

Even if a soluble human B7-2-Ig fusion protein were able to able to provide the second costimulatory signal necessary to induce an immune response – which Applicants do not concede – Freeman provides no suggestion that such human B7-2-Ig fusion protein was selected from a library of polynucleotides encoding B7-2 variants and that it had a better ability to costimulate an immune response than a polynucleotide from which the library was created.

2) The Short PCT Does Not Teach or Suggest Recursive Sequence Recombination.

In its original Decision, the Board correctly concluded that the Short PCT did not teach or suggest recursive sequence recombination. See BPAI Decision (Paper No. 181), e.g., ¶¶148-149 at p. 129, line 8 to p. 132, line 16; ¶¶170-176 at p. 142, line 10 to p. 147, line 4. In its subsequent Memorandum, the Board takes the position that "[t]he Short PCT directs persons skill in the art to utilize recursive sequence mutations, including recursive sequence recombinations, to produce novel DNA which encodes a polypeptide having desirably enhance properties." BPAI Memorandum, p. 25, line 22 to p. 26, line 2. In support of this revised view, the Board cites p. 33, line 35 to p. 35, line 17 of the Short PCT, alleging this passage describes "methods for obtaining polynucleotides having an optimized phenotype comprising: a) creating a library of recombinant polynucleotides; and b)

screening the library to identify those polynucleotides having a variant phenotype, whereby optimization is achieved by recursive sequence recombination." BPAI Memorandum, p. 16, line 14 to p. 18, line 7. Applicants strongly traverse these findings and submit that the Short PCT does not teach or suggest recursive sequence recombination as set forth in the instant application.

Recursive sequence recombination as defined in the instant application refers to methods of evolving gene sequences by using successive cycles of particular sequence recombination formats described in the application to generate a population of mutant gene sequences that have some sequence identity to each other, but which differ from one another by having different mutations and/or different combinations of mutations. The resultant population of evolved mutant genes can be screened for those having a desired property or characteristic. See the specification, including at, but not limited to, e.g., p. 18, line 4 to p. 19, line 2 and p. 20, lines 2-3. The instant application specifically refers to a number of patent applications and scientific references that present exemplary formats and examples for recursive sequence recombination. Some such formats are sometimes referred to as DNA shuffling, evolution, or molecular breeding. See, e.g., the specification at p. 18, line 18 to p. 19, line 2.[4]

The instant application describes one format of recursive sequence recombination in which first and second forms of a nucleic acid encoding a protein are recombined to generate a library of mutant polynucleotides. The library of mutant polynucleotides can be screened to identify an optimized mutant polynucleotide having a desired property of interest, such as an enhanced ability to modulate an immune response compared to a form of the nucleic acid from which the library was created. An optimized mutant polynucleotide can then be recombined with a further form of the nucleic acid, which is the same or different from the first and second forms used to create the library,

[4] The meaning of the term "recursive sequence recombination" as defined in the instant application was carefully considered by the Board during the Interference. The Board's original Decision (Paper No. 181) sets forth the proper construction of this term, consistent with that outlined above, based on the specification and additional evidence submitted during the Interference. See BPAI Decision (Paper No. 181), e.g., ¶135 at p. 121, line 19 to p. 123, line 11 and ¶173 at p. 143, line 10 to p. 144, line 1. For example, in properly construing this term, the Board relied on expert testimony of Dr. Lewis L. Lanier, an expert in the field of immunology who testified on behalf of Senior Party Punnonen. See Second Declaration of Lewis L. Lanier, Ph.D., ¶¶35-36 (Punnonen Exhibit 1079 in Interference No. 105,188). In contrast, in its subsequent Memorandum, the Board interprets the term wholly out of context, without consideration of Applicants' specification, and without regard to the evidence on this issue expressly made of record during the Interference.

to produce a further library of mutant polynucleotides. The further library can be screened to identify at least one further optimized mutant polynucleotide having a desired property, such as a further improved ability to modulate an immune response compared to a form of the nucleic acid from which the library was created. See the specification, including at, but not limited to, e.g., p. 17, line 1 to p. 19, line 2 and original claims 5 and 6.

The instant application also presents one particular embodiment in which recursive sequence recombination is used to generate optimized costimulatory mutant B7-1 or mutant B7-2 proteins having increased activity through CD28 ligand and decreased activity through CTLA-4 ligand and improved ability to activate T cells. See the specification, including at, but not limited to, e.g., p. 50, line 6 to p. 53, line 20; and Fig. 10.

In a preferred exemplary embodiment, different forms of the nucleic acid substrate used to create a library are, e.g., B7-1 cDNAs from various species, such as human, rhesus monkey and rabbit. See, e.g., the specification at p. 50, line 28 to p. 51, line 2; and p. 66, line 16 to p. 68, line 23. The human B7-1 gene, a rhesus monkey B7-1 gene, and a rabbit B7-1 gene are recombined to generate a library of chimeric mutant B7-1 nucleic acids which contain nucleotide residues from each of the three forms of the nucleic acid substrate used to generate the library. The library can then be screened to identify an encoded mutant B7-1 chimeric protein having an improved property, such as an improved ability to activate T cells compared to the proteins encoded by the substrate nucleic acids. Further recombination and screening procedures can be conducted to obtain a further optimized chimeric B7-1 protein having further improved function. See, e.g., p. 66, line 16 to p. 68, line 23; p. 7, lines 12-13 and 16-17; and Figs. 13 and 15.

Applicants respectfully submit that the Short PCT does not remotely teach or suggest any recursive sequence recombination method described in the instant application. The passage in the Short PCT cited by the Board – p. 33, line 35 to p. 35, line 17 – plainly does not disclose recursive sequence recombination. In this passage, Short describes making a parental clone that contains two different nucleotide sequences and replicating each of the two different nucleotide sequences contained within a single clone separately under conditions that allow mutations to occur in either of the two nucleotide sequences. Short PCT, p. 33, line 37 to p. 34, line 28. Recombination between the two different nucleotide sequence populations is then allowed so as "*to reassociate mutant*

nucleotide sequences to form new pairs of the two sequences that were not paired in the original mutated, replicated population." *Id.*, p. 33, lines 29-33 (emphasis added). Short acknowledges this is a simple combinatorial method in which new combinations of the two different nucleotide sequence populations are made. *Id.*, p. 33, lines 4-37.

An example of this combinatorial method is provided by Short at p. 35, lines 1-17. In the example, the two different nucleotide sequences are designated "A" and "B," respectively, and the parental clone containing nucleotide sequence A and nucleotide sequence B is designated clone A/B, indicating that the two different types of nucleotide sequences are linked together. *Id.*, p. 35, lines 1-4. Mutations are made in either sequence A or sequence B by replicating parental clone A/B under mutating conditions that allow mutations to occur in either sequence A or sequence B. The following variant clones are formed: A1/B, A/B1, A2/B1, A/B2, and A3/B. *Id.*, p. 35, lines 1-9. Variant A1/B, for example, contains a mutated A nucleotide sequence (designated A1) and an unmutated B nucleotide sequence.

With this procedure, though, Short notes some combinations do not occur, such as combinations A1/B2, A2/B, A2/B2, A3/B1, and A3/B2. *Id.*, p. 10-11. Short explains, however, that such combinations can be made by allowing the variants A1/B, A/B1, A2/B1, A/B2, and A3/B and the non-mutated parental clone A/B to recombine by swapping one particular A sequence with another A sequence, and/or swapping one B sequence with another B sequence. As a result, new combinations of the A and B sequences, such as A1/B2, A2/B, can be made. *Id.*, p. 35, lines 10-17.

The Short PCT does not suggest <u>any</u> of the recursive sequence recombination methods described in the instant application in which, for example, successive cycles of particular sequence recombination formats are used to evolve an initial set of two or more related genes (such as genes from different species encoding proteins of the same type – e.g., B7-1 genes of different species) to generate a library of chimeric gene sequences that differ from one another by having different mutations and/or different combinations of mutations. Short does not disclose or suggest any method in which two related nucleic acids are recombined to produce a population of new mutant nucleotide sequences having new mutations which *result from the recombination (exchange of nucleic acids).* For example, there is no suggestion in Short to recombine one form of an A nucleotide sequence (e.g., A1) with a different form of the A sequence (e.g., A2) such that

nucleotide residues of A1 and A2 are exchanged and a new mutant sequence having nucleotide residues from both A1 and A2 is generated.

Notably, in the Short PCT, the site of recombination is the point between the A and B gene sequence in the A/B clone – that is, the point at which an A sequence is linked to a B sequence. Recombination of one A/B clone with another clone simply involves swapping intact A sequences, and/or swapping intact B sequences. That is, one A sequence (e.g., A, A1) is swapped with a different A sequence (e.g., A2, A3) and one B sequence (e.g., B, B1) is swapped with different B sequence (e.g., B2, B3). No new mutant A sequence is created by the recombination process itself – no matter how many times the process is repeated. Similarly, no new mutant B sequence results from the recombination process – no matter how many times the process is repeated.

The two passages in the Short PCT at p. 34, lines 29-30 and p. 35, lines 11-17, which the Board emphasizes with underlining (see BPAI Memorandum, p. 17, lines 18-19 and lines 40-45), confirm the fact that Short's recombination process is merely a reassociation whereby new combinations of pre-existing A and B sequences are made. There is no suggestion whatsoever that any mutation in an A sequence results from the reassociation of different A sequences; nor is there any suggestion any mutation in a B sequence results from the reassociation of different B sequences.

For at least these reasons, Applicants submit that the Short PCT does not teach or suggest recursive sequence recombination as set forth in either claim 47 new claim 49.

C. The Combined Teachings of the Freeman PCT and the Short PCT in View of the State of the Art Described by Stemmer Do Not Teach or Suggest the Method Defined by Canceled Claim 47 or New Claim 49.

In addition to finding that the Freeman PCT discloses all of the limitations of method set forth in claim 47 except "wherein optimization is achieved by recursive sequence recombination" and the Short PCT discloses methods for obtaining polynucleotides having an "optimized phenotype whereby optimization is achieved by recursive sequence recombination," the Board further finds that the Stemmer reference provides a description of the knowledge and skill of a person of ordinary skill at the time. The Board concludes that:

> [T]he combined teachings of the Freeman PCT, the Short PCT, and Stemmer reasonably would have led persons having ordinary skill in the art to optimize the modulatory effect of B7-2 variants encoded by novel DNA produced by homologous recombination by: a) creating a library of recombinant DNA encoding B7-2, b) promoting sequence recombination in the recombinant DNA library, c) screening the library for novel recombinant DNA which exhibits an enhanced ability to modulate an immune response induced by a genetic vaccine vector, and optimizing the enhanced ability of the novel recombinant DNA to modulate the immune response by recursive DNA sequence recombination, and reasonably expect success."

BPAI Memorandum, p. 26, lines 3-14.

The Examiner bases the rejection of claim 47 on these findings by the Board. Applicants respectfully traverse the rejection of claim 47 and submit nevertheless that the rejection is overcome by new claim 49 for at east the following reasons.

Three requirements must be met to establish a *prima facie* case of obviousness. First, the cited references must teach all of the limitations of the claims. MPEP § 2143.03. Second, there must be some particular suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine their teachings to produce the claimed invention. *Id.* Third, it must be demonstrated that there is a reasonable expectation of success of carrying out the claimed invention based on the teachings of the cited references. *Id.* The teaching or suggestion to combine and the reasonable expectation of success must both be found in the references themselves and not based on Applicants' disclosure. *Id.*

Applicants submit that the requirements for a *prima facie* case of obviousness have not been met. None of the cited references – taken alone or in any combination – teaches or suggests the method recited in claim 47. First, as demonstrated above, the Short PCT clearly does not teach or suggest recursive sequence recombination as described in the instant application, such as methods involving successive cycles of sequence recombination to generate new mutant nucleotide sequences having mutations which result from recombination (exchange of nucleic acids). The Short PCT merely discloses recombination events that involve making newly associated pairs (new combinations) of two different existing A and B sequences are made.

Furthermore, as shown above, the Freeman PCT does not teach or suggest all of the aspects of the method of claim 47 except for "whereby optimization if achieved by recursive sequence

recombination." The Freeman PCT does not teach any method involving making a library of mutant polynucleotides and screening such library for an optimized polynucleotide encoding a costimulator that is a B7-1 or B7-2 mutant having an altered activity through CD28 and CTLA-4 and an enhanced ability to modulate an immune response compared to a nucleic acid from which the library was created. Freeman merely discloses cloning wild-type human B7-2 or murine B7-2 using well-known cloning expression techniques involving the preparation of human cDNA library or murine cDNA library and the screening of such library using the known CD28 and CTLA-4 ligands to identify and isolate the human B7-2 gene or the murine B7-2 gene. The teachings of the Stemmer reference do not rectify the inadequacies of the disclosures of the Freeman and Short PCTs.

Based on the teachings of these three references, one of skill would not have had a reasonable expectation of successfully carrying out the method of claim 47.

For at least these reasons, Applicants submit that a proper *prima facie* case of obviousness has not been made – and cannot be made -- and that the rejection of claim 47 under § 103 is improper.

The rejection of claim 47 has been mooted by its cancellation, and new claim 49 is now presented. Applicants submit that that new claim 49 is clearly patentable over the teachings of the Freeman PCT, the Short PCT, and the Stemmer reference – taken alone or in any combination. For example, none of these references, taken alone or together, discloses a method for optimizing an optimized immunomodulatory polypeptide which comprises creating a library of mutant polynucleotides from (1) a set of one or more nucleic acids encoding a B7-1 (CD80) protein or (2) a set of one or more nucleic acids encoding a B7-2 (CD86) protein, wherein nucleic acids of the set differ from each other in at least two nucleotides. Neither the human cDNA library nor the murine cDNA library disclosed in Freeman is a library of mutant polynucleotides created from a set of one or more nucleic acids encoding a B7-1 protein or set of one or more nucleic acids encoding a B7-2 protein wherein the nucleic acids of the set differ from each other in at least two nucleotides.

None of these references – nor any combination thereof – remotely suggests screening such a library of mutant polynucleotides to identify an optimized mutant polynucleotide that encodes a mutant B7-1 or mutant B7-2 protein which is a costimulator that has (1) an improved ability to activate a T cell response induced by a genetic vaccine vector, (2) an increased activity through

CD28 and (3) a decreased activity through CTLA-4, compared to a B7-1 or B7-2 protein encoded by a nucleic acid from which the library was created. The Freeman PCT, for example, does not suggest any method for obtaining a mutant B7-2 protein that has *an increased activity through CD28 and a decreased activity through CTLA-4* compared to a B7-2 protein encoded by a nucleic acid from which the library was created, as provided in new claim 49. Freeman does not suggest any B7-2 variant that has an *increased activity through CD28* (by, e.g., having an increased binding affinity for CD28), as compared to, e.g., a wild-type B7-2 protein. Nor does Freeman imply any B7-2 variant that has a *decreased activity through CTLA-4* (by, e.g., having a lower binding affinity for CTLA-4), as compared to, e.g., a wild-type B7-2 protein. The method defined by claim 49 particularly specifies a mutant B7-2 or mutant B7-1 protein having new activities nowhere disclosed or suggested in the Freeman PCT. Additionally, none of these references suggests such a method whereby optimization is achieved by recursive sequence recombination.

Furthermore, Applicants submit that one of skill would have plainly understood the limited teachings of Freeman and Short and would not have found any suggestion or motivation in the references themselves to combine their teachings.

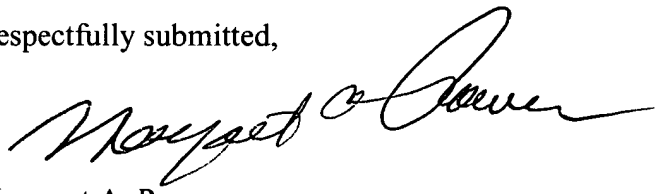
Moreover, based on the combined teachings of these references, one of ordinary skill in the art at the time the application was filed would not have had any reasonable expectation of successfully carrying out the method specifically defined by claim 49. The Freeman PCT teaches that wild-type human B7-1 and B7-2 bind both CTLA-4 and CD28, but that each binds CTLA-4 more strongly than either binds CD28. See Freeman PCT, p. 2, lines 3-4 and p. 90, lines 23-31. Given Freeman's teachings, one of skill would not have had any reasonable expectation that a functional costimulatory mutant B7-1 or mutant B7-2 protein having an improved ability to activate a T cell response, an increased activity through CD28, and a decreased activity through CTLA-4 compared to, e.g., a wild-type B7-1 or B7-2, could be obtained.

For at least these reasons, Applicants submit that the method of claim 49 is patentable over the teachings of the Freeman PCT, the Short PCT, and/or the Stemmer reference. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe the claim now pending in this application is in condition for allowance. In the event that any issues of substance remain, Applicants hereby request an Examiner interview prior to the preparation of any additional written action by the Examiner. Please feel free to call the undersigned at (650) 298-5809 to arrange for an Examiner's interview or to discuss any concerns or questions regarding this paper or the application in general.

Respectfully submitted,



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